HEPATIC CIRCULATION AND HEPATIC FUNCTION DURING ANAESTHESIA AND SURGERY*

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THE HEPATIC DAMAGE which may follow anaesthesia and surgery is often considered to be a direct toxic effect of the anaesthetic agent used [1–5] However, there is a possibility that this injury, usually centrolobular necrosis, and often indistinguishable from damage due to infection,[6–8] is produced by liver hypoxia of systemic or local circulatory origin The effect of prolonged systemic hypoxia in the occurrence of liver necrosis is well known during shock,[9] cardiac failure,[10] respiratory insufficiency,[11] asphyxia,[12] low atmospheric pressure,[13] and thyrotoxicosis [14] Whether short periods of systemic hypoxia, such as might occur during surgery, can also damage the liver is unknown at the present time The hepatic circulatory changes associated with surgery and their role in the development of this lesion are also unknown

The sequence of events leading to the production of centrolobular necrosis by carbon tetrachloride, chloroform, and other anaesthetic agents is the subject of much discussion From biochemical data, Calvert, Moore, and Brody[15 16] conclude that the first event in CCl_4 poisoning is interference with the hepatic circulation producing ischaemic anoxia and necrosis Experiments of Brody and co-workers suggest that the hepatic circulation is protected by sympatholytic drugs, adrenalectomy, or spinal cord section [17 18] It is postulated that high oxygen concentration offers similar protection [19 20] Brauer and co-workers,[21 22] however, believe that the primary action of the hepatotoxic agents is the production of a cellular lesion and only secondarily a circulatory impairment Therefore, in the absence of circulatory changes, the initial injury would not develop into necrosis, protection would be provided by alteration of the course of the lesion rather than by prevention of the initial damage

If drugs alone are being considered, the site and type of the injury may be related to the method of administration The injection of carbon tetrachloride through the portal vein produces diffuse haemorrhagic liver necrosis[23] which differs from the centrolobular necrosis produced when the drug is inhaled Using this difference as a basis, Glynn and Himsworth strongly support the circulatory impairment theory [24] Carbon tetrachloride and chloroform, when administered through the systemic circulation, affect the central part of the hepatic lobules, theoretically the least exposed to the drug and also the least oxygenated part of the hepatic tissue

It seems clear from the available information that regardless of any hepatotoxic effect, the hepatic damage that might follow the administration of some anaesthetic agents is directly related to hepatic hypoxia Whether this injury is

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mediated through their systemic or local hepatic circulatory effects is unknown.

The subject of this study is, first, to determine alterations in the liver circulation under various surgical conditions, second, to standardize a hepatic lesion and observe its inherent circulatory changes, and third, to determine the effect of these circulatory changes on the hepatic lesion (The last two parts—II, The Effect of Various Anaesthetic Agents, and III, Chloroform-Induced Liver Damage —are in press in this *Journal*)

I HEPATIC HAEMODYNAMICS UNDER SURGICAL CONDITIONS

Hepatic blood flow may be measured using indirect methods based on the Fick principle [25 26] These studies have limited value since it is not possible to differentiate between the portal venous flow and the hepatic artery blood flow, moreover, no continuous recordings are possible Other authors use *in situ* perfusion of the liver,[27 28] which gives important information on the pressure/flow relationship, but interferes with the normal hepatic circulation A third possibility, that used in this study, is the use of electromagnetic blood-flow meters[29–31] placed around the hepatic artery[32] and the portal vein Although the surgical preparation and anaesthesia can by themselves interfere with the hepatic circulation, this last method may give reliable and valuable information, provided a simple surgical technique and light anaesthesia are employed

This paper describes a technique utilizing electromagnetic blood-flow meters placed around the hepatic artery and the portal vein with as little interference to intraperitoneal structures as possible Observations on alterations in blood gases, systemic blood pressure, and the effects of some catecholamines on the hepatic blood flow and the portal O_2 and CO_2 partial pressures are also presented

Method

Seventy mongrel dogs averaging 18 kg in weight were used Each animal was anesthetized with an intravenous injection of thiopental (20 mg/kg) and artificially ventilated with 100 per cent oxygen by means of an endotracheal tube and a Bird Mark VIII respirator Muscular paralysis was achieved by intermittent intravenous injections of succinylcholine, 20 mg every 30 minutes

Right atrial (central venous) pressure and abdominal aortic pressures were determined by means of plastic catheters advanced through the femoral vessels Portal venous pressure was measured with a polyethylene catheter introduced through a gastric vein The mean systemic arterial pressure was obtained by electrical integration of the arterial pressure pulse Hepatic artery vascular resistance was calculated as the ratio of mean systemic arterial pressure in mm Hg to hepatic artery blood flow in flow units per minute These flow units are presented as cubic centimeters per minute in the various figures However, all calculations were made as relative changes from control observations in the same experiment, and in no case were these compared to the flows in different experiments In some experiments cardiac output was measured by the same electromagnetic blood-flow technique

Lead II of the electrocardiograph and a fronto–occipital electro-encephalographic lead were recorded along with the other variables on a Sanborn 150 oscillograph

After exposing the hepatic hilus, a 2-mm electromagnetic flow-meter probe was carefully placed around the hepatic artery A second probe was used in the portal vein The hilus was exposed through an incision in the left 11th intercostal space and incision of the left diaphragm (Fig 1).

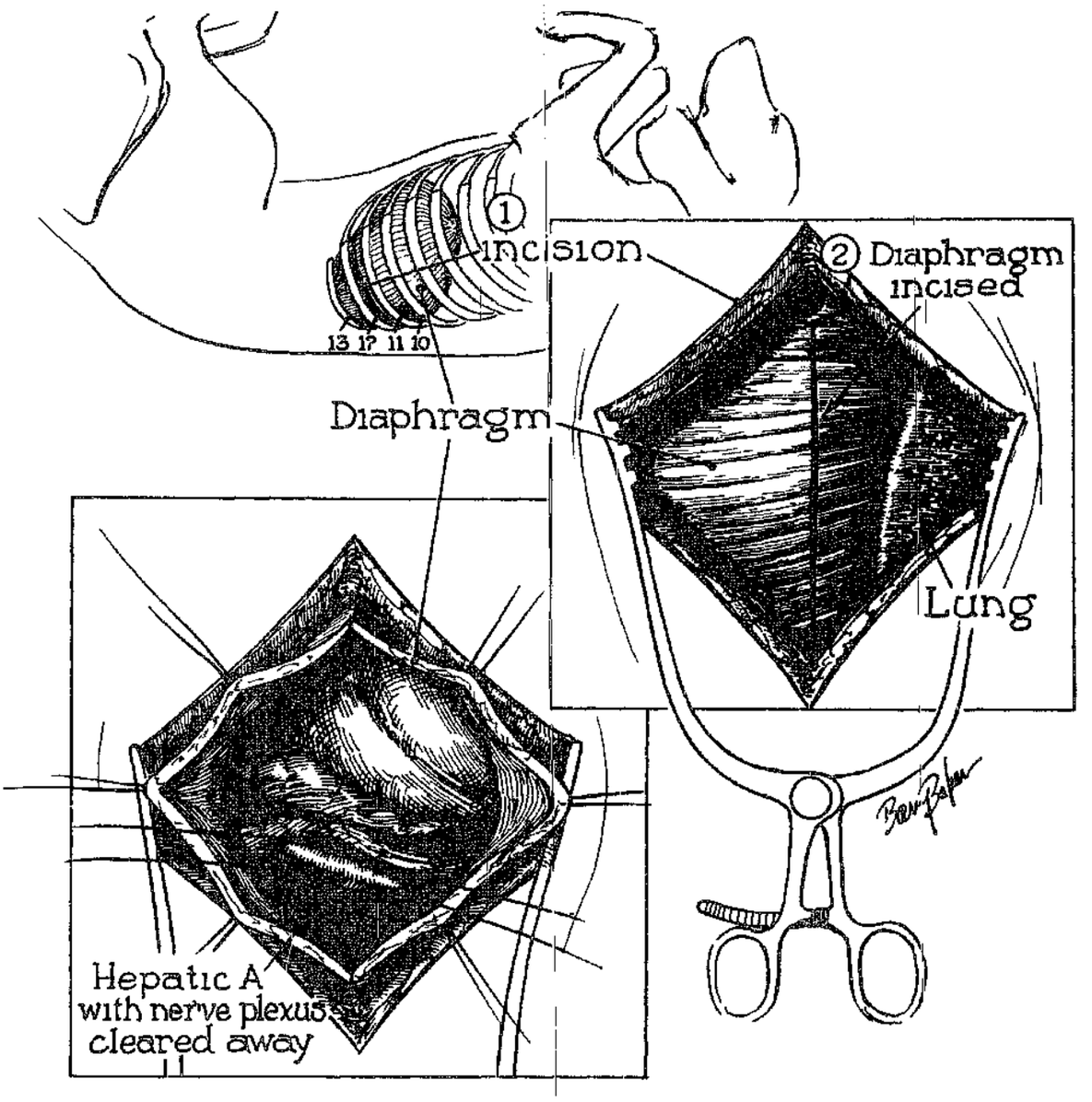

FIGURE 1 Surgical technique for localization of the hepatic hilus

The principle and technique of the electromagnetic method for blood-flow determinations used in the present studies have been described in detail elsewhere [29–31] In this report, flow was expressed in relative changes from control observations, the error introduced thus being small (±5%)

Systematic arterial and portal vein blood samples were analysed frequently for pH, pCO_2, and pO_2, using a polarograph Each animal was maintained for at least one hour at normal pH, pCO_2, and pO_2 Modifications of the parameters obtained during this period were considered as the normal variability, or base-line of this preparation

The following observations were made in groups of 3 to 10 dogs (A) the effects of increased arterial pCO_2 (>48 mm Hg), (B) the administration of 100 per cent O_2 at 1 and 2 atmospheres of pressure, (C) metabolic acidosis, (D) hepatic trauma as produced by compression (retractor) of the hepatic hilus, (E) haemorrhage (10–20 c c /kg), (F) cold (8° C) and warm (27° C) blood transfusion

The following drugs were administered intravenously to groups of 5 dogs epinephrine (1–3 μg /kg), norepinephrine (0 2–1 μg /kg), methoxamine (Vasoxyl) (0 1 mg /kg), mephentermine (Wyamine) (0 15 mg /kg), acetylcholine (0 2 mg /kg), metaramine (Aramine) (0 1 mg /kg), isoproterenol hydrochloride (1 μg /kg), and ephedrine sulphate (2 mg /kg).

The following agents were injected into the portal vein to groups of 5 dogs histamine phosphate (0 02 mg), acetylcholine (1 mg), epinephrine (4 μg), norepinephrine (2 μg), isoproterenol hydrochloride (1 μg)

The effect of total sympathetic block by epidural anaesthesia was determined in 10 animals The hepatic hilus was infiltrated with 5 c c of 1 per cent lidocaine in four animals

Results

1 *General Pattern of Hepatic Blood Flow*

Although hepatic blood flow, that is, hepatic artery blood flow plus portal vein blood flow, is readily modified under various circumstances, a general pattern emerged Portal venous blood flow is mostly passive and follows systemic circulatory changes, mainly in central venous and systemic arterial pressures Hepatic arterial blood flow is, with some limitations, independent of systemic arterial blood pressure and responsive to the various pharmacological agents as well as to blood pH, pO_2, and pCO_2 Differences between the arterial and portal blood pO_2 and pCO_2 are mostly dependent upon portal blood flow, which in turn depends upon the systemic venous and arterial pressures

The blood flow in the hepatic artery is phasic with waves of irregular frequency, one every 30 seconds to 3 minutes These phasic changes are characterized by irregularity of appearance and variable volume per wave unit as seen in Figure 2 The waves in the hepatic artery flow disappear following unskilled surgery, metabolic acidosis, or deep anaesthesia

2 *Effects of Alteration in Blood Gases*

The pO_2 in the portal vein is 80–100 mm Hg under ventilation with 100 per cent oxygen and 40–80 mm Hg under ventilation with air However, great variation in these values was observed Hypotension decreased the portal pO_2 and increased the portal pCO_2 in proportion to the portal blood flow reduction (Table I)

The inhalation of 100 per cent O_2 at 1 or 2 atmospheres of pressure had no significant effect on the portal or hepatic artery blood flows The only significant change was observed in the portal pO_2 This pressure increased from 60 mm Hg, room air, to 600 mm Hg at 2 atmospheres of pressure with 100 per cent O_2,

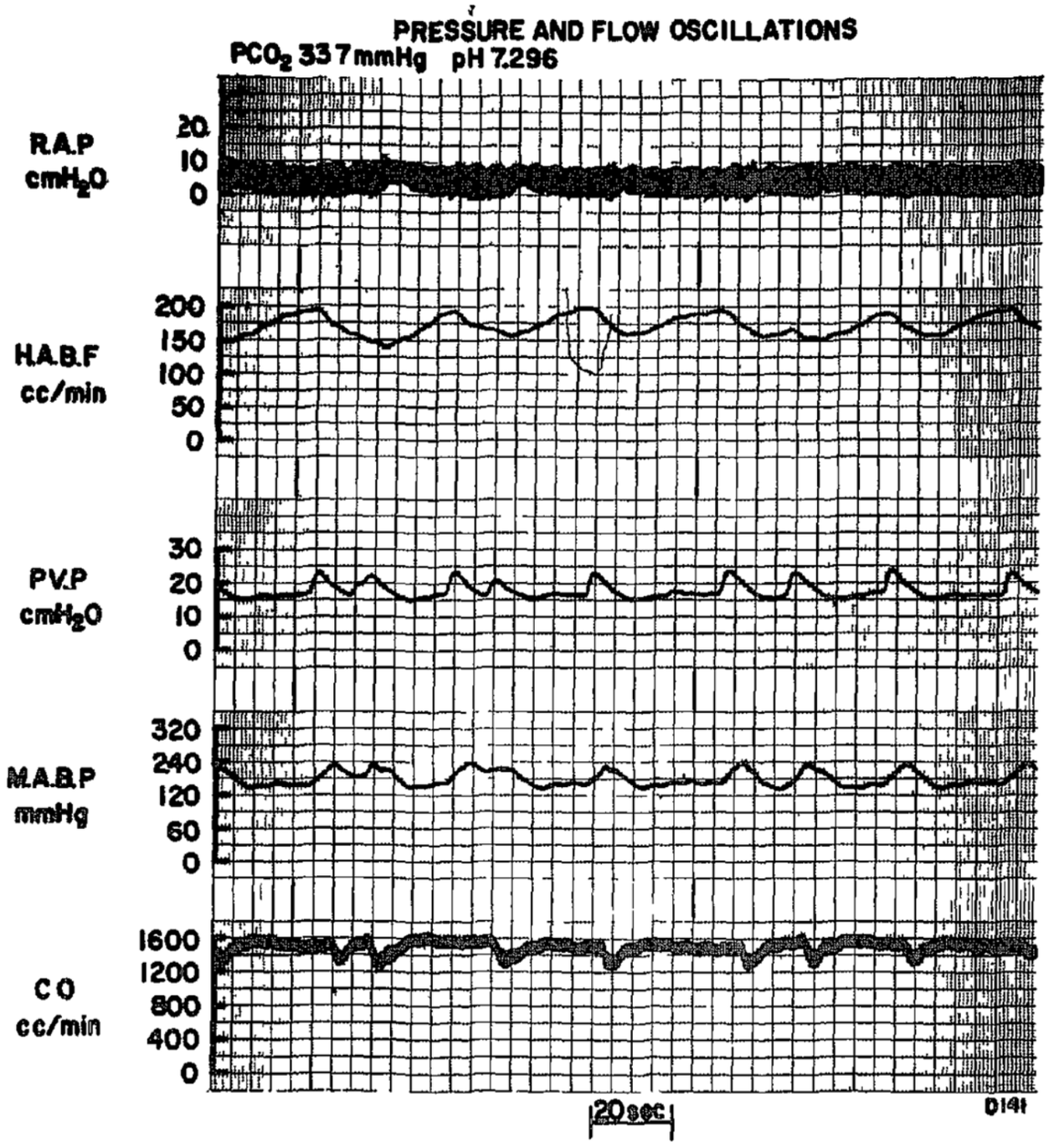

FIGURE 2 Blood flow oscillations in the hepatic artery R A P = right atrial pressure H A B F = hepatic artery blood flow P V P = portal venous pressure M A B P = Mean arterial blood pressure C O = cardiac output

although there was some individual variation The effect of the splenic circulation on the portal pO_2 values is currently under study in this laboratory

Carbon dioxide had a significant effect on hepatic blood flow (Table II) It decreased hepatic artery vascular resistance and increased its flow Portal pressure and portal pO were increased as result of a higher portal blood flow However the administration of CO_2 under metabolic acidosis or maximum sympathetic stimulation had no significant effect on hepatic haemodynamics or decreased the hepatic artery and portal vein blood flow according to its systemic effect (These observations are presented and compared with the effect of hypercarbia under various anaesthetic conditions in work now in preparation for publication)

TABLE I

CHANGES IN PORTAL pO_2 AND pCO_2 AS RELATED TO PORTAL BLOOD FLOW AND ARTERIAL OXYGEN TENSION

Air			100% O_2 Control			100% O_2 After blood loss			100% O_2 1 atm			100% O_2 2 atm		
PBF	pO_2 (mm Hg)	pCO_2 (mm Hg)	PBF	pO_2 (mm Hg)	pCO_2 (mm Hg)	PBF	pO_2 (mm Hg)	pCO_2 (mm Hg)	PBF	pO_2 (mm Hg)	pCO_2 (mm Hg)	PBF	pO_2 (mm Hg)	pCO_2 (mm Hg)
80	P 39 8	P 43 2	130	P 79 8	P 43 3	20	P 33	P 94 5	95	P 64 6	P 38 7	70	P 116	P 84
	A 40 1	A 39 8		A 391	A 33 2		A 394	A 44 5		A 346	A 32 4		A 1 004	A 69 3
80	P 48 2	P 56 5	80	P 130	P 66	60	P 51 9	P 48 1	60	P 92 1	P 44 7	45	P 596	P 48 7
	A 53	A 53 8		A 431	A 59 5		A 514	A 42 7		A 513	A 37 2		A 1156	A 43 3
75	P 61	P 48 1	90	P 81	P 44 8	10	P 64	P 55	35	P 106	P 43 3	50	P 334	P 51 1
	A 68	A 436		A 399	A 43		A 436	A 45 6		A 510	A 35 8		A 1154	A 40
50	P 47 9	A 53 2	50	P 76	P 48	20	P 40	P 55	45	P 80 9	P 55 7	55	P 172	P 60
	A 80 4	P 436		A 527	A 43		A 453	A 39		A 501	A 44 5		A 1147	A 48 5

PBF = portal vein blood flow in flow units
P = portal
A = arterial

TABLE II

	% change	Standard error	$P <$
Haemorrhage (15 c c /kg)			
HABF	−17 0	13 3	0 10
HAVR	+ 5 1	11 0	0 80
PP	−10 7		
Carbon dioxide (pCO_2 63 8 mm Hg)			
HABF	+28 8	15 2	0 005
HAVR	−20 3	3 4	0 005
PP	+20 8	0 8	0 01
Total sympathetic block (epidural anaesthesia)			
HABF	−35 8	11 2	0 001
HAVR	− 9 3	18 3	0 25
PP	−14 4	0 4	0 001

HABF = hepatic artery blood flow
HAVR = hepatic artery vascular resistance
PP = portal vein pressure

Metabolic acidosis (pH < 7 30 at normal pCO_2) following haemorrhage, hypotension, or hypoxia greatly decreased the hepatic artery blood flow in all experiments in which they occurred pH correction with sodium bicarbonate improved the hepatic circulation (Fig 4)

3 *Effects of Haemorrhage*

During the early stages of haemorrhage (10–15 c c /kg), hepatic arterial blood flow did not fall, however, it fell after further bleeding (20 c c /kg) and/or haemorrhagic acidosis The portal pressure and flow were depressed from the beginning of the haemorrhage (Table I) A blood transfusion given immediately after severe bleeding (20 c c /kg) corrected this hepatic circulatory

impairment Cold (8° C) blood administration (20 c c. in 3 minutes) resulted in a transient reduction of blood flow in the hepatic artery lasting 1 to 5 minutes

4 *Effects of Sympathetic Block*

Total sympathetic block decreased hepatic blood flow The "hepatic waves" disappeared (Table II and Fig 3) The hepatic circulation subsequently recovered

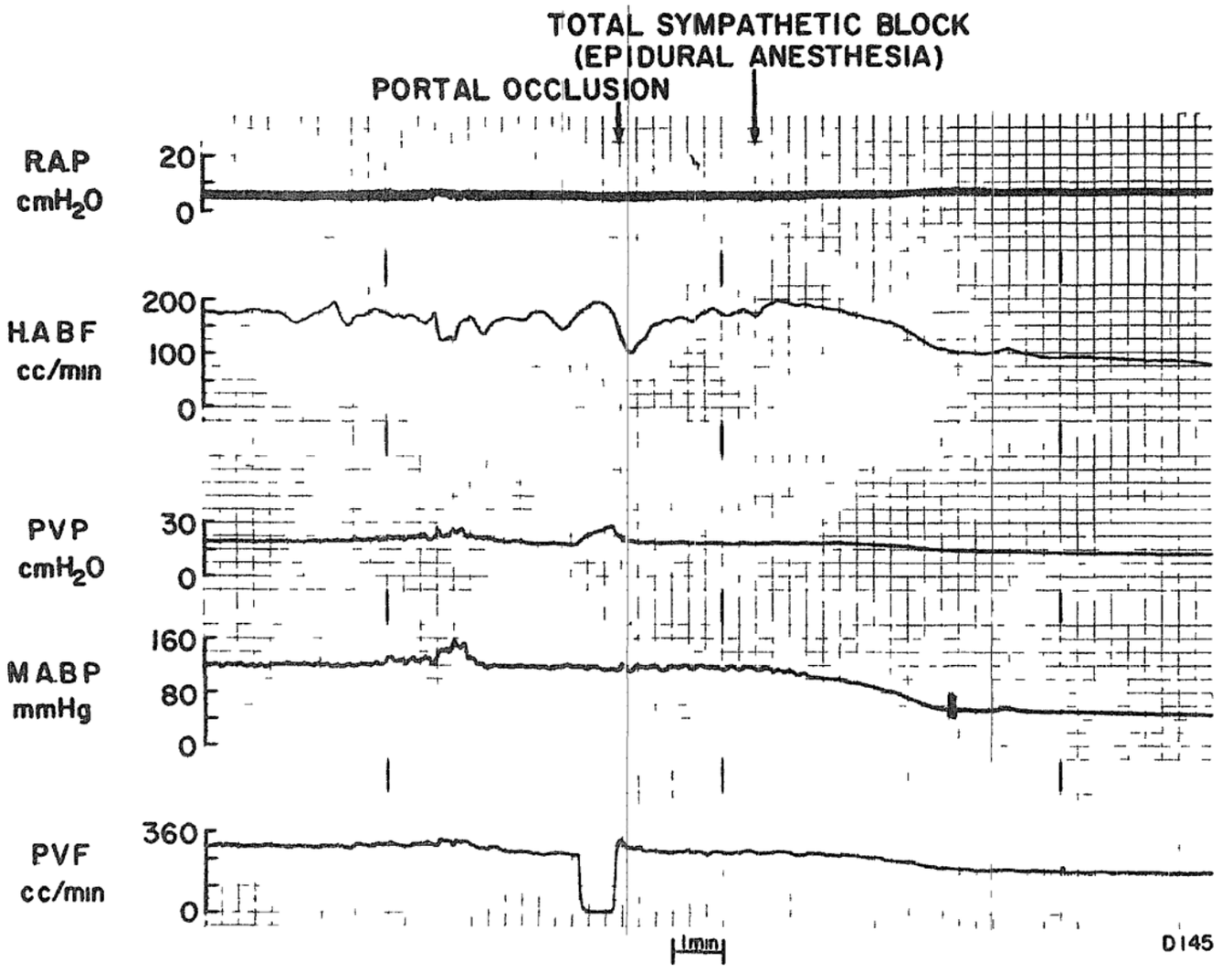

FIGURE 3 Total sympathetic block abolished the hepatic artery blood-flow oscillations and depressed hepatic blood flow P V F = portal vein blood flow, other abbreviations as in Figure 2

5 *Effects of Local Trauma*

Traumatic compression of the hepatic hilus in 10 animals decreased the hepatic artery blood flow, its recovery was slow Infiltration of the hepatic hilus with local anaesthesia in five dogs or total sympathetic block in three animals had a minor protective effect against this type of trauma

6 *Effects of Administration of Vasopressor Drugs*

The *intravenous* administration of epinephrine increased hepatic artery blood flow in all experiments * This was noteworthy in two depressed animals (low cardiac output and arterial hypotension, Fig 5). However, its *intraportal* admini-

*Changes in portal blood flow were inconsistent, it mostly increased

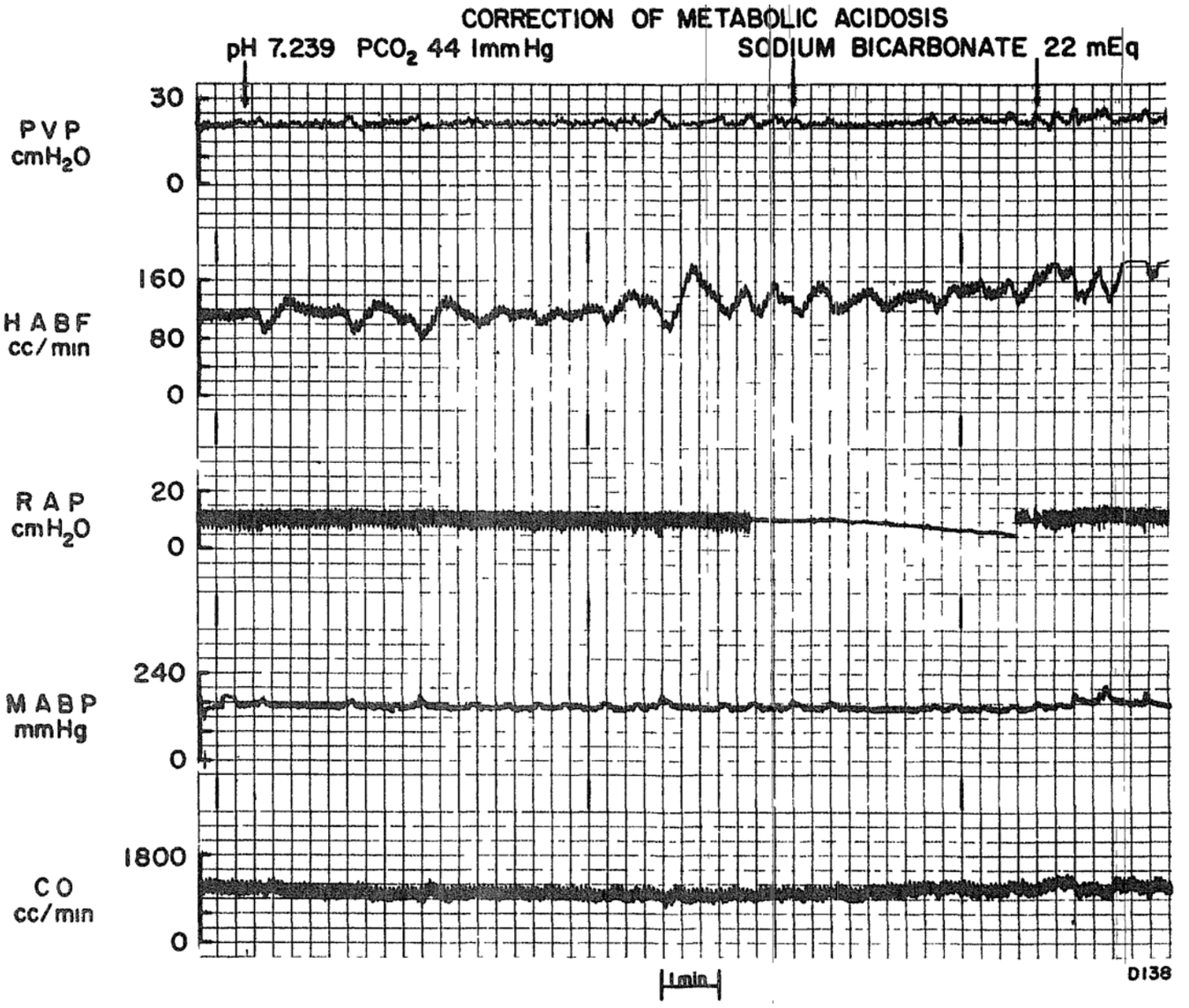

FIGURE 4 Metabolic acidosis depressed hepatic artery blood flow Its correction restored the flow (Abbreviations as in Figure 2)

stration produced vasoconstriction of the hepatic artery and the portal vein (Fig 6)

Similar but less marked results were obtained with norepinephrine when administered systematically or through the portal vein.

Table III summarizes the results obtained after intravenous and intraportal administration of various pharmacological agents The changes noted were found consistently Intraportal injections of histamine or acetylcholine increased the hepatic artery blood flow with no significant effect elsewhere Methoxamine increased the systemic blood pressure but decreased the hepatic artery blood flow Mephentermine increased the hepatic arterial and portal venous blood flow Metaraminol increased hepatic artery blood flow and portal vein blood flow Isoproterenol decreased the resistance in both the hepatic artery and the portal vein, while opposite results were obtained with ephedrine

DISCUSSION

The arterial blood supply of the liver is capable of compensatory adjustments and has some degree of independence of arterial blood pressure It is responsive

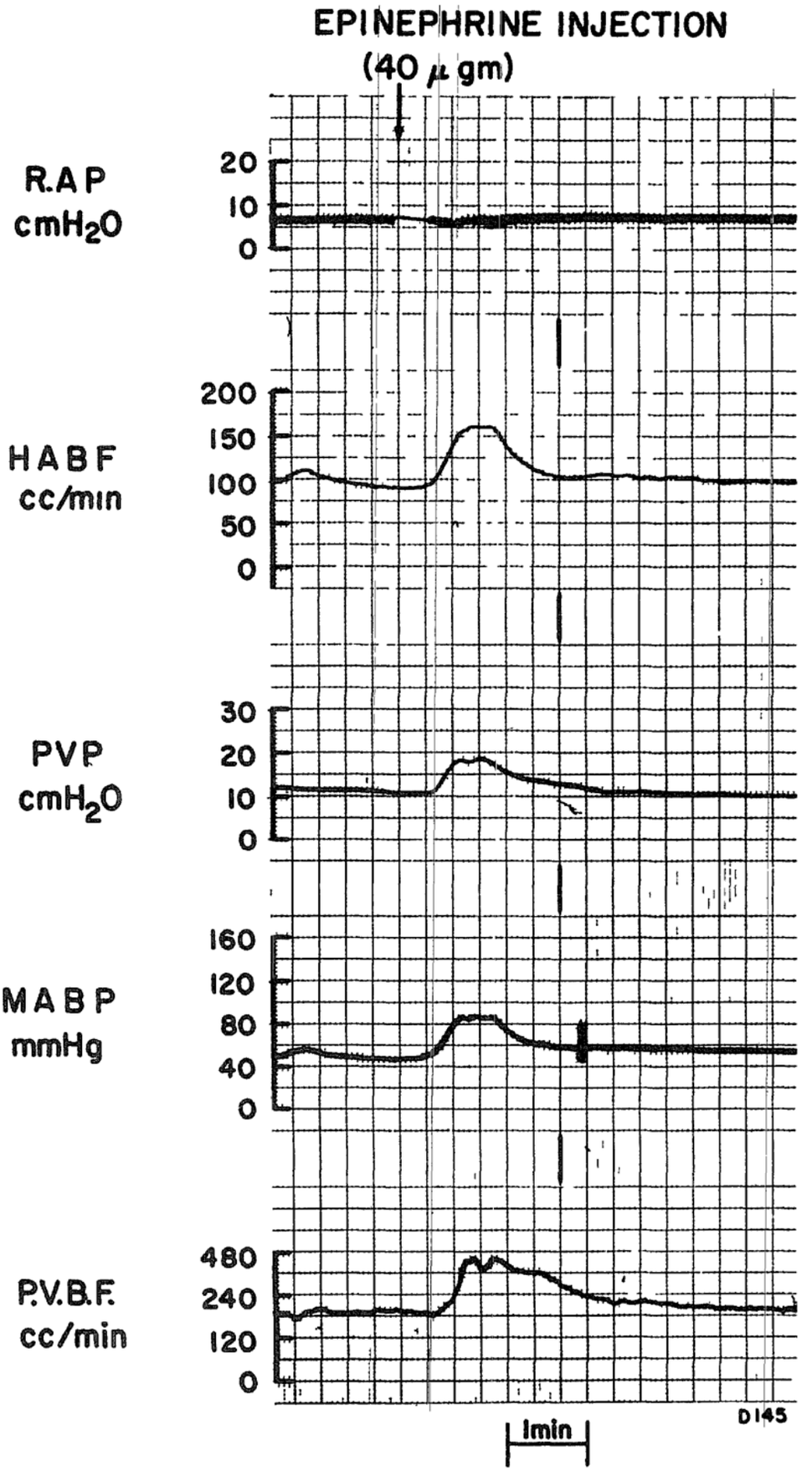

FIGURE 5 The systemic administration of epinephrine, especially in depressed animals, improved the hepatic circulation P V B F = portal vein blood flow, other abbreviations as in Figure 2

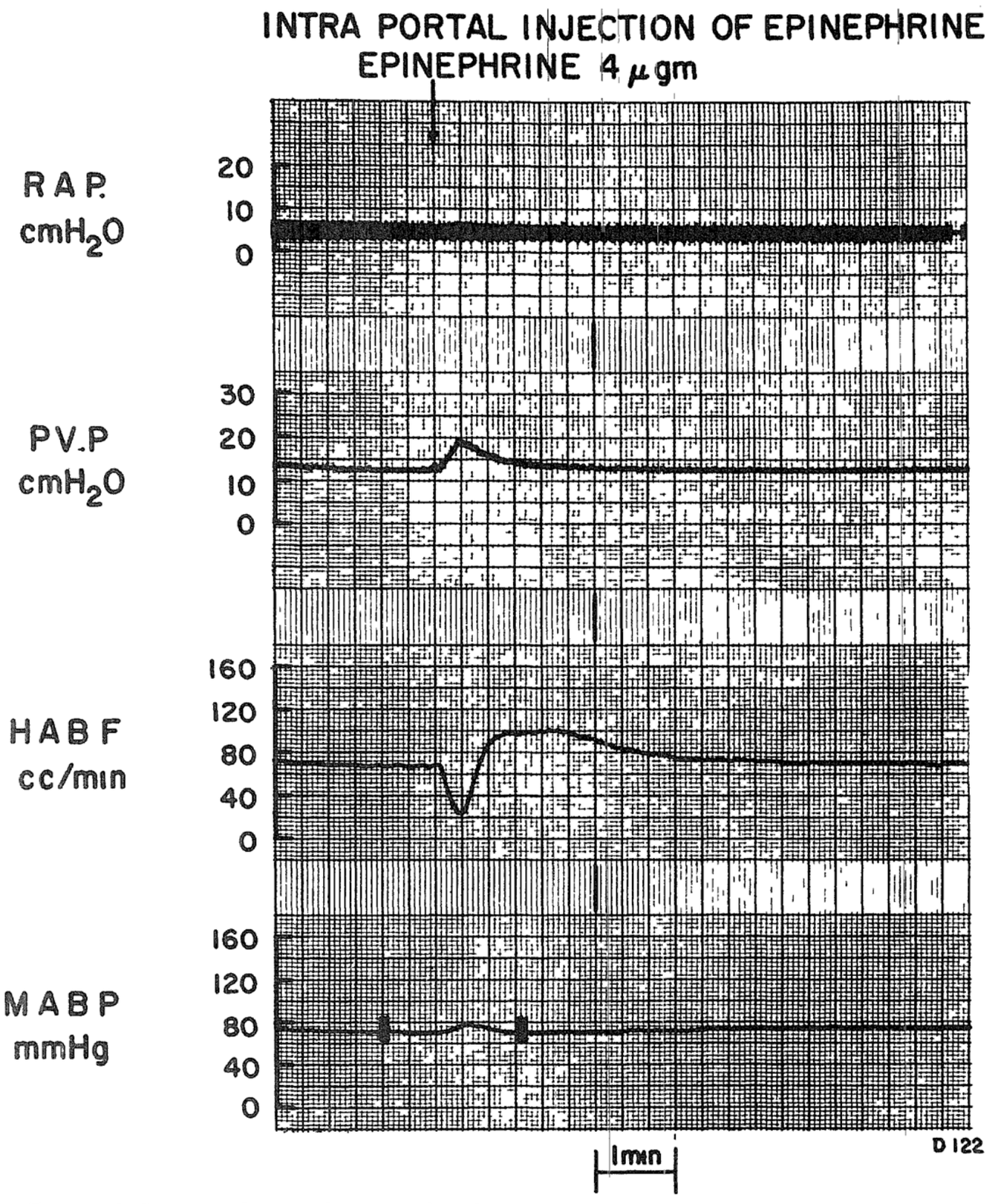

FIGURE 6 Intraportal epinephrine produced constriction of the portal vein and the hepatic artery, there was a postinjection vasodilatation in the latter vessel Abbreviations as in Figures 1 and 2

to changes in blood pH and pCO_2 On the other hand, portal blood flow is passively dependent upon systemic arterial blood pressure and central venous pressure The difference between these two vessels is evident during mild haemorrhage, in which case the arterial flow is sustained and the portal flow decreased Preservation of the arterial blood flow of the liver, during systemic depression (lower cardiac output and/or arterial hypotension) as might occur

TABLE III

DIRECTIONAL CHANGES IN THE HEPATIC CIRCULATION AS PRODUCED BY VARIOUS PHARMACOLOGIC AGENTS AND METABOLIC ACIDOSIS

	HABF		HAVR		PVBF	
	IV	IP	IV	IP	IV	IP
Epinephrine	↑	↓	↓	↑	↑	↓
Norepinephrine	↑	↓	↓	↑	↑	↓
Histamine		↑			–	–
Acetylcholine	↓	↑	↓	↓	↓	
Metabolic acidosis			↑			
Metoxamine (Vasoxyl)	↓	↓	↑	↑		
Mephentermine (Wyamine)	↑	↑	↓	↓	↑	–
Metaraminol (Aramine)	↑	↑	↓	↓	↑	–
Isoproterenol (Isuprel)	↑	↑	↓	↓	↑	–
Ephedrine	–	↓	↑	↑	–	–

HABF = hepatic artery blood flow
HAVR = hepatic artery vascular resistance
PVBF = portal vein blood flow
↑ = increase
↓ = decrease
IV = intravenous injection
IP = intraportal injection
— = inconsistent results

during or immediately after surgery, is important in the prevention of hepatic damage since during systemic arterial hypotension the oxygen supply through the portal vein is decreased while the pCO_2 of this vein is increased Thus, hepatic O_2 consumption becomes more dependent on the hepatic artery blood flow

Systemic administration of catecholamines (epinephrine and norepinephrine) improves the hepatic circulation This could explain the early response of the hepatic artery to haemorrhage and also to carbon dioxide inhalation, similar observations have been reported previously [33–35] However, these two agents produce local vasoconstriction of the hepatic vessels when given intraportally

An intrinsic control of the hepatic circulation is suggested by the vasoconstriction produced by trauma, this reaction has been reported before[36] and can also be obtained by local sympathetic nervous stimulation [27] This may be an explanation for the "outflow block," or great increase in hepatic vascular resistance, reported during the first 45 minutes of liver perfusion experiments

The effect of carbon dioxide is basically similar to that obtained in a previous study in man[37] and dog, in which CO_2 stimulated or depressed hepatic blood flow according to the depth of anaesthesia and kind of anaesthetic agent and the systemic arterial pressure changes

The hepatic artery blood-flow oscillations ("hepatic waves") could be produced by a vaso-active agent, released in the mesenteric or splenic circulation The function and importance of this oscillation is unknown at present Previous reports describe oscillations but of different nature since flow determinations were not made in a continuous manner [38]

These observations confirm the presence of several mechanisms by which hepatic oxygen supply can be modified during a surgical operation, independent of the anaesthetic agent or the depth of anaesthesia

Summary

A technique for hepatic blood-flow determinations is described The hepatic artery blood flow was found to have some degree of independence of the arterial blood pressure, while the portal flow followed systemic circulatory changes Trauma to the liver, metabolic acidosis, or total sympathetic block depressed hepatic artery blood flow Carbon dioxide, epinephrine, or norepinephrine increased the hepatic artery blood flow, however, this effect was related to their systemic circulatory changes Several factors decreased portal oxygen saturation

Résumé

L'auteur décrit une technique de détermination des débits sanguins hépatiques Tandis que le débit de l'artère hépatique semblait être indépendant de la pression artérielle, celui de la veine porte suivait les variations circulatoires systémiques

Les traumatismes au foie, l'acidose métabolique, le blocage complet du système sympathique diminuaient le débit de l'artère hépatique Le bioxyde de carbone en l'absence d'acidose métabolique, l'épinéphrine, la norépinéphrine augmentaient le débit de l'artère hépatique, cependant il faut rattacher ce dernier effet à leurs changements circulatoires systémiques Parmi les nombreux facteurs diminuant la saturation en oxygène du sang porte, la diminution du débit sanguin dans la veine porte était le plus important

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